Attorney Docket No. CS-120
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	Group Art Unit: Unknown
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TALOR	)	Examiner: Unknown
	)	
Serial No. 10/611,914	)	
	)	
Filed: July 03, 2003	)	

For: **A METHOD OF PRE-SENSITIZING CANCER PRIOR TO TREATMENT WITH RADIATION AND/OR CHEMOTHERAPY AND A NOVEL CYTOKINE MIXTURE**

PETITION TO MAKE SPECIAL UNDER 37 C.F.R. § 1.102

Commissioner for Patents
Alexandria, VA 22313-1450

Sir:

Applicant submits herewith a petition to make special the above-identified application under 37 C.F.R. § 1.102 as an invention relating to a treatment of cancer. The fee under 37 C.F.R. 1.17(h) is submitted herewith along with a statement that a pre-examination search was made, a copy of each reference found in the pre-examination search, a detailed discussion of how the invention is patentable over each of the cited references and a statement of how the invention contributes to the treatment of cancer.

Accordingly, Applicant respectfully requests that the captioned application be accorded special status and receive the benefit of accelerated examination.

REMARKS

Presently pending claims 1-41 relate to a novel cytokine mixture and a method for pre-sensitizing cancer prior to chemotherapy, radiation therapy or immuno-therapy using the novel cytokine mixture.

The cytokine mixture is a serum-free and mitogen-free mixture comprised of specific ratios of cytokines such as IL-1β, TNF-α, IFN-γ and GM-CSF to Interleukin 2 (IL-2), which is effective in inducing cancerous cells to enter a proliferative cell cycle phase selected from the group of G_1, S, G_2 and M thereby increasing their vulnerability to chemotherapy, radiation therapy and immuno-therapy.

The presently claimed concentrations and methods in combination with chemotherapy, radiation therapy and immuno-therapy increases the overall success rate of these cancer therapies. Moreover, preliminary evidence demonstrates that the presently claimed invention dramatically improves disease free survival. For example, a small cohort of 8 patients treated with the claimed methods and compositions had a 0% recurring tumor rate at 24 months after treatment despite a known recurrence rate of 50% in patients at 18-24 months.

Pre-Examination Search

Applicant submits that a pre-examination search was made in the U.S. Patent Office Public Search Room in the following classes: Class 424, subclasses 85.1, 85.2, 85.4 and 85.5; Class 514, subclasses 2 and 21; and Class 530, subclass 351. Additionally, keyword searching was conducted on the search computer in U.S. Patents, U.S. Published Applications and JPO and EPO databases.

The following patents relating to treatment methods and agents involving cytokines applied to diseases, particularly cancer, are enclosed.

U.S. 4,863,727 Zimmerman et al. '727

U.S. 4,879,111 Chong

U.S. 5,098,702 Zimmerman et al. '702

U.S. 5,425,940 Zimmerman et al. '940

U.S. 6,051,218 McBride

U.S. 6,420,335 Weichselbaum et al.

U.S. 6,423,313 Esmon et al.

U.S. 6,509,313 Smith

U.S. 6,551,588 McBride

U.S. Pub 2002/0150552 Lau et al.

U.S. Pub 2002/0173538 Shiao

DE 19506362 Kirchner

Discussion of the References

4,863,727 ("Zimmerman et al. '727") teaches a combination therapy using Interleukin-2 and Tumor Necrosis Factor wherein anti-tumor activity is augmented by sequentially administering a synergistically effective amount of TNF and IL-2 or of TNF and IFN-β or of TNF, IL-2 and IFN-β. See col. 3, lines 18-36.

The presently claimed invention is patentable over Zimmerman et al. '727 because the novel and unobvious ratios of the specific cytokines of IL-2 to IL-1β, IL-2 to TNF-α, IL-2 to IFN-γ and IL-2 to GM-CSF are not taught. Instead, Zimmerman et al. '727 only teaches a vague description of "synergistically effective amounts" of TNF and IFN-β, which does not include the presently claimed IL-1β, TNF-α, IFN-γ and GM-CSF. Furthermore, Zimmerman et al. '727 fails to teach the method of inducing cancerous cells to enter a proliferative cell cycle phase selected from the group of G_1, S, G_2 and M thereby increasing their vulnerability to follow-on chemotherapy, radiation therapy and immuno-therapy.

5,098,702 ("Zimmerman et al. '702") is a divisional of 4,863,727 ("Zimmerman et al. '727") and similarly fails to anticipate or render obvious the claimed invention.

5,425,940 ("Zimmerman et al. '940") is a divisional of

4,863,727 ("Zimmerman et al. '727") and similarly fails to anticipate or render obvious the claimed invention.

4,879,111 ("Chong") teaches a treatment of microbial infections with a combination of TNF and IL-2 or TNF and IFN-γ. See col. 5, lines 30-57 and claim 10.

The presently claimed invention is patentable over Chong because the novel and unobvious ratios of the specific cytokines of IL-2 to IL-1β, IL-2 to TNF-α, IL-2 to IFN-γ and IL-2 to GM-CSF are not taught. Instead, Chong only teaches activity units of IL-2 and TNF. Furthermore, Chong fails to teach the method of inducing cancerous cells to enter a proliferative cell cycle phase selected from the group of G_1, S, G_2 and M thereby increasing their vulnerability to follow-on chemotherapy, radiation therapy and immuno-therapy.

6,051,218 ("McBride '218") only discloses a method of radiosensitizing a tumor by contacting the tumor with interleukin-**3**, GM-CSF or G-CSF. See col. 5, line 10 through col. 6, line 14.

Nothing in McBride '218 relates to novel and unobvious ratios of the specific cytokines of IL-**2** to IL-1β, IL-2 to TNF-α, IL-2 to IFN-γ and IL-2 to GM-CSF. Furthermore, McBride '218 fails to teach the method of inducing cancerous cells to enter a proliferative

cell cycle phase selected from the group of G_1, S, G_2 and M thereby increasing their vulnerability to follow-on chemotherapy, radiation therapy and immuno-therapy.

6,551,588 ("McBride '588") is a continuation of 6,051,218 ("McBride '218") and similarly fails to anticipate or render obvious the claimed invention.

6,420,335 ("Weichselbaum et al.") teaches sensitization of cancer cells to radiation therapy through the use of anti-angiogenic factors. Although Weichselbaum et al. discloses embodiments where a cell is further sensitized by contact with cytokine in combination with an anti-angiogenic factor, the cytokine is IL-**12** and not the presently claimed ratios or mixture of IL-**2**. See col. 5, lines 26-58; col. 12, lines 11-29.

Weichselbaum et al. fails to teach the novel and unobvious ratios of the specific cytokines of IL-2 to IL-1β, IL-2 to TNF-α, IL-2 to IFN-γ and IL-2 to GM-CSF and is instead concerned with application of angiostatin. Moreover, nothing in Weichselbaum et al. relates to the method of inducing cancerous cells to enter a proliferative cell cycle phase selected from the group of G_1, S, G_2 and M thereby increasing their vulnerability to follow-on chemotherapy, radiation therapy and immuno-therapy.

6,423,313 ("Esmon et al.") teaches compositions and methods for inhibition tumor growth where the active agent is a compound blocking the protein C system. Preferably the active agent is provided in combination with a cytokine such as TNF, INF-γ, IL-1, IL-2 or GM-CSF. See generally col. 3 and 4; See also col. 9, line 33 to col. 11, line 8.

Esmon et al. fails to teach the novel and unobvious ratios of the specific cytokines of IL-2 to IL-1β, IL-2 to TNF-α, IL-2 to IFN-γ and IL-2 to GM-CSF. Furthermore, Esmon et al. fails to teach the method of inducing cancerous cells to enter a proliferative cell cycle phase selected from the group of G_1, S, G_2 and M thereby increasing their vulnerability to follow-on chemotherapy, radiation therapy and immuno-therapy.

6,509,313 ("Smith") teaches a method of stimulating the immune system with low doses of cytokines. Smith teaches various forms of cytokine compositions such as solutions, suspensions, powders, tablets, emulsions, encapsulated particles, and topical compositions for unit dosage.

Although Smith discloses IL-2, IL-12, IL-15, IFN-α, IFN-γ, IFN-β, TNF-α, nowhere are the critical ratios of the specific cytokines of IL-2 to IL-1β, IL-2 to TNF-α, IL-2 to IFN-γ and IL-2

to GM-CSF disclosed. Furthermore, Smith fails to teach the method of inducing cancerous cells to enter a proliferative cell cycle phase selected from the group of G_1, S, G_2 and M thereby increasing their vulnerability to follow-on chemotherapy, radiation therapy and immuno-therapy.

2002/0150552 ("Lau et al.") discloses cytokine mixtures for use in cancer treatment with 2 or more cytokines selected from IL-2, IL-12, IL-15, IFN-α, IFN-β, IFN-γ, IFN-Ω, TNF-α, NKEF, NKSF, TRAIL, GM-CSF. See paragraph 0113. Lau et al. also teaches that the total cytokine dose administered is adjusted so that any one cytokine component is administered at a lower dose of a normal dose of that cytokine when administered alone. See paragraph 0115.

Nevertheless, the novel and unobvious ratios of the specific cytokines of IL-**2** to IL-1β, IL-2 to TNF-α, IL-2 to IFN-γ and IL-2 to GM-CSF are not taught. Furthermore, Lau et al. fails to teach the method of inducing cancerous cells to enter a proliferative cell cycle phase selected from the group of G_1, S, G_2 and M thereby increasing their vulnerability to follow-on chemotherapy, radiation therapy and immuno-therapy.

2002/0173538 ("Shiao") teaches a method for sensitizing cancer cells to cancer therapies by arresting cancer cell growth at G0/G1

and G2/M stages of the cell cycle. However, a Mevalonate Reducing Compound or HMG-CoA reductase inhibitors are taught to arrest cell growth, not cytokines. Clearly, the novel and unobvious ratios of the specific cytokines of IL-2 to IL-1β, IL-2 to TNF-α, IL-2 to IFN-γ and IL-2 to GM-CSF are not taught.

The method of inducing cancerous cells to enter a proliferative cell cycle phase selected from the group of G_1, S, G_2 and M thereby increasing their vulnerability to follow-on chemotherapy, radiation therapy and immuno-therapy is also not taught.

DE19506362 ("Kirchner") teaches a method of producing cytokine mixtures where peripheral blood mononuclear cells are isolated from whole blood and then incubated with monoclonal antibody OKT3 and then collected in a supernatant wherein interleukin-2 is later added to the supernatant.

Based on the Abstract, it does not appear that the novel and unobvious ratios of the specific cytokines of IL-2 to IL-1β, IL-2 to TNF-α, IL-2 to IFN-γ and IL-2 to GM-CSF are taught. Instead, Kirchner appears to only relate to a production process for making a natural batch of cytokines. Furthermore, the method of inducing cancerous cells to enter a proliferative cell cycle phase selected from the group of G_1, S, G_2 and M thereby increasing their

vulnerability to follow-on chemotherapy, radiation therapy and immuno-therapy does not appear to be disclosed.

CONCLUSION

In light of the foregoing, Applicant submits that all the requirements for according special status have been met and respectfully request accelerated examination. Favorable action with an early allowance of the presently pending claims is earnestly solicited. If any further communication to expedite the prosecution of the application is required, the Examiner is invited to contact the Applicant's representative at the telephone number given below.

Respectfully submitted,

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